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CASE REPORT

COVID-19-associated euglycemic diabetic ketoacidosis in a patient with type 2 diabetes on SGLT2 inhibitor: a case report

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Abstract

Type 2 diabetes mellitus (DM) patients are at high risk for the development of severe COVID-19. Euglycemic diabetic ketoacidosis (eu-DKA) is a rare life-threatening complication associated with the use of SGLT2 inhibitor that may be unnoticed, particularly in a pandemic setting, due to the absence of significant hyperglycemia, delaying its treatment. In this report, we describe a case of a 56-year-old patient who presented an elevated anion gap metabolic acidosis during a SARS-CoV-2 infection and was diagnosed with SGLT2-associated euglycemic diabetic ketoacidosis. COVID-19 may increase patients' insulin demand, present gastrointestinal symptoms, and increase the production of ketone bodies. This situation can be worsened in susceptible diabetic patients on SLGT2 inhibitors, due to the persistent glycosuria, which can cause volume depletion. Recently some authors recommended that insulin-deficient patients or those using SGLT2 inhibitors should monitor for ketosis using available home testing kits in case of infections and should discontinue the medication in case of COVID-19. Given the increased use of this drug class in the management of type 2 DM patients due to its reduction of cardiovascular risk, we set out to emphasize the importance for the medical community to consider the possibility of eu-DKA on SARS-CoV-2-infected patients using SLGT2 inhibitors, so physicians can provide these patients with appropriate therapy promptly.

Keywords Coronavirus disease 2019 (COVID-19) · Type 2 diabetes · Euglycemic diabetic ketoacidosis · SGLT2 inhibitor

Introduction

Patients with type 2 diabetes mellitus (T2DM) seem to have increased risk for more severe SARS-CoV-2 infections and higher mortality rate, regardless of age, especially when there is poorly controlled blood glucose [1–3].

Diabetic ketoacidosis (DKA) is an acute and potentially lethal complication of both type 1 diabetes mellitus and T2DM, defined by the triad of hyperglycemia (> 250 mg/dL), high anion gap metabolic acidosis, and increased plasma ketones [4]. However, DKA can occur without marked hyperglycemia, often < 200 mg/dL, which is called euglycemic DKA (eu-DKA) [5].

In May 2015, the Food and Drug Administration (FDA) warned that treatment with sodium–glucose cotransporter-2 (SGLT2) inhibitors may increase the risk of ketoacidosis [6]. Several publications reporting the association between these drugs and eu-DKA have been published since then [5, 7, 8]. The frequency of reported DKA events related to SGLT2 inhibitor treatment in T2DM patients is less than 0.1% [9]. Eu-DKA is a life-threatening emergency in those patients, presumably poorly recognized and underreported due to the absence of significant hyperglycemia. Although some mechanisms for this adverse effect have been proposed [10], further investigation is needed to understand its causes.

We describe a case of eu-DKA associated with COVID-19 in an individual with T2DM in the setting of SGLT2 inhibitor therapy. As COVID-19 pandemic has grown a great public health issue, this report is particularly relevant considering the role of diabetes in the severity of SARS-CoV-2 infections and the possibility of delayed diagnosis of eu-DKA and its adverse metabolic consequences [2, 3, 5].

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Case report

A 56-year-old man with a history of systemic arterial hypertension and T2DM presented to an Emergency Department (ED), brought by his relatives, with myalgia, fever, and cough. Symptoms began 5 days prior admission to the ED, situation in which the patient was in poor general condition, requiring support to walk. The patient denied history of alcohol or illicit drug use, diarrhea, vomiting, bleeding, or previous surgeries.

At that time, the patient was on losartan 50 mg once a day, metformin 850 mg twice a day, and empagliflozin/linagliptin − 10 mg + 5 mg, 1 pill once a day.

Clinical examination revealed body weight of 72 kg, height 1.65 m, BMI 26.4 kg/m^2, tachypnea with a respiratory rate of 26 breaths/minute, drowsiness, a Glasgow Coma Scale of 14, heart rate of 105, systolic blood pressure of 100 mmHg, diastolic blood pressure of 70 mmHg, a mean blood pressure of 80 mmHg, and good peripheral perfusion. Due to COVID-19 pandemic scenario, the health workers were wearing their personal protective equipment, including facial masks, which made the evaluation of the presence of acetone smell impracticable.

Chest computed tomography showed ground-glass opacification (Fig. 1). The rapid testing panel for respiratory viruses that included influenza A and B was negative and the RT-PCR test for SARS-CoV-2 was positive.

On admission, he presented metabolic acidosis with elevated anion gap, arterial pH 7.28, pCO2 19 mmHg, bicarbonate 8.9 mmol/L, and base excess − 15.7. The blood analysis showed creatinine 1.19 mg/dL, blood urea nitrogen (BUN) 14.93 mg/dL, hemoglobin 12 g/dL, 13,300 leukocytes, 1300 lymphocytes, sodium 132 mEq/L, potassium 5.6 mEq/L, chlorine 99 mEq/L, C-reactive protein 20.20 mg/dL (normal value < 0.3 mg/dL), glucose 118 mg/dL, and hemoglobin A1c (HbA1c) 7.2%.

The blood tests were performed after an intravenous hydration therapy with 20 ml/kg made at the ED, before the patient's transfer to the intensive care unit (ICU).

Given the patient's use of empagliflozin, an oral antidiabetic agent belonging to the SGLT2 inhibitor class, and its association with the risk of eu-DKA [9], we proceeded a ketone bodies investigation with an isolated urine sample, which showed up positive. β-hydroxybutyric acid level was not available.

At ICU, intravenous regular insulin was started at 4 units per hour (0.05 UI/kg/h) with 10% glucose solution at initial flux of 120 ml/h. Once the patient was not with hyperglycemia, we did not proceed with an administration of an intravenous bolus dose of insulin. The plasma glucose concentration goal was ~ 11.1–13.9 mmol/L. Potassium levels were monitored every 4 h and the replacement was made using KCL 19,1% as needed. The types of fluids and their flow rate were administered based on plasma glucose levels [5, 11]. The total insulin dose in the first 8 h was 48 units.

After starting therapy, the patient had a marked recovery in his clinical status, with improvement of electrolyte abnormalities, urinary ketones, and acidosis (Table 1). Concerning the treatment for COVID-19 infection, clinical support measures were performed, which included oxygen therapy using a high-flow nasal cannula for 8 days, with no need

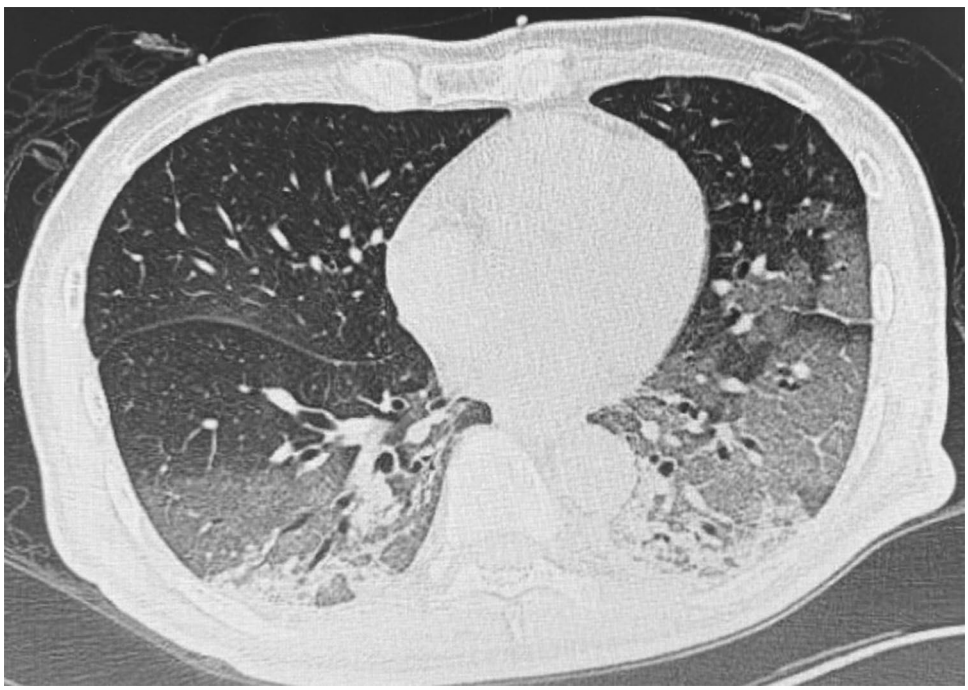

Fig. 1 The patient's chest computed tomography showing ground-glass opacification

Table 1 Laboratory values from the patient before and after treatment for diabetic ketoacidosis

Blood analyses	31/03/2020 22:12 Before endovenous insulin	01/04/2020 06:11 8 h after endovenous insulin
pH	7.28	7.35
PaO_2 (mmHg)	123	99
PCO_2 (mmHg)	19	34
Sodium bicarbonate (mmol/L)	8.9	18.8
Base excess (mmol/L)	− 15.7	− 6.0
Arterial lactate (mg/dL)	14	12
Sodium (mEq/L)	132	134
Chlorine (mEq/L)	99	–
Potassium (mEq/L)	5.6	3.1
BUN (mg/dL)	14.93	–
Uric acid (mg/dL)	32	–
Creatinine (mg/dL)	1.12	1.19
Glucose (mg/dL)	118	96
HbA1C	7.2%	
Urinary Ketones	++	+
Urinary Glucose	+++	+++
C-reactive protein (mg/dL)	20.20	–
Hemoglobin (g/dL)	13.5	13.9
Leukocytes (μ/L)	13,900	13,300
Lymphocytes (μ/L)	1280	1300
Platelets ((μ/L)	230,000	235,000

for invasive mechanical ventilation. In addition, antibiotic therapy with azithromycin 500 mg was administered once a day for the first 5 days of hospitalization, and prophylaxis for venous thromboembolism was carried out with subcutaneous sodium enoxaparin 40 mg once a day during the entire hospitalization. The patient remained in the ICU for 12 days and was discharged after 20 days at hospital, with improvement in his general condition and breathing pattern.

Discussion

SGLT2 inhibitor drugs are strongly recommended by different societies for the reduction of cardiovascular risk in T2DM patients [12, 13], as these drugs reduce the incidence of heart failure and the risk for major cardiovascular events related to atherosclerosis [12]. Therefore, it has become a class of drugs widely used in clinical practice.

COVID-19 infection may increase insulin demand and present gastrointestinal symptoms, such as diarrhea, nausea, and anorexia [14], leading to volume depletion and increased fat breakdown, thus resulting in increased ketone bodies production. This situation can be worsened in susceptible diabetic patients on SLGT2 inhibitors due to the persistent glycosuria which can also cause volume depletion [15, 16].

Ketosis and ketoacidosis are complications described in the context of COVID-19. In a study that analyzed 658 patients admitted for COVID-19, 42 had ketosis on admission, of which only 15 were previously diabetic and 3 developed DKA. It is still unclear whether or not there is a higher prevalence of DKA and which mechanism of COVID-19 can induce ketoacidosis [16]. Both DKA and COVID-19 have high levels of inflammatory markers, including IL-6, which have been related to the severity of SARS-CoV-2 infection and with the development of DKA [17].

Eu-DKA is a rare complication in T2DM patients on SGLT2 inhibitors, with a range of 0.16–0.76 events per 1000 patients-year [9, 18, 19], but recently some authors recommended that insulin-deficient patients or those using SGLT2 inhibitors should monitor for ketosis using available home testing kits in case of infections.

Mirabelli et al. recommended to withdraw SGLT2 inhibitor in those T2DM patients with severe β-cell insufficiency who are on insulin therapy at initial symptoms of COVID-19 illness [15]. Parlermo et al. and Bornstein et al. had a broader approach and suggested discontinuing SGLT2 inhibitors in the context of COVID-19 infection at the first signs of the illness, regardless of insulin use status, in an attempt to avoid the development of ketoacidosis and acute metabolic decompensation [17, 18]. Nevertheless, it is described on medical literature that the pharmacological effects of these drugs can persist for several days [20]. Consequently, despite the discontinuation of the drug within the first signs of COVID-19, the patients may still develop eu-DKA and they need to be monitored.

There are two case reports of eu-DKA in the setting of SARS-CoV-2 infection and SGLT2 inhibitor use [17, 21], but we would like to emphasize some differences this report presents. The first difference is that the patient investigated in the present case report has T2DM and developed eu-DKA even without being on previous use of insulin. The second particularity is that the T2DM patient described by Palermo et al. [15] developed eu-DKA after 24 h of hospitalization, whereas in ours, the patient was already presented to ED with this condition, which reminds us of the importance of evaluating this possibility at the admission of the patient who is using SGLT2 inhibitors.

Once recognized, the management of eu-DKA includes the same triad as the classic DKA: volume resuscitation, potassium and insulin replacement, but with the difference that fluids containing glucose are needed in the initial stage and not later as in the classic DKA [5, 17].

During the actual pandemic scenario, physicians may not initially recognize eu-DKA due to relative euglycemia and delay its treatment. We set out to emphasize the risk of this acute complication in COVID-19-infected patients using

SGLT2 inhibitors, even if they are not insulin-dependent or have already discontinued the medication. The medical community should keep in mind the possibility that a SARS-CoV-2-infected patient with a high anion gap metabolic acidosis and that is using that drug class can be undergoing eu-DKA, so physicians can provide this patient with appropriated treatment.

All procedures conducted herein were in accordance with the ethical standards of the institutional and national committees on human experimentation, as well as with the 1964 Helsinki Declaration and later versions. Informed consent or a substitute thereof was obtained from the patient included in this study.

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Compliance with ethical standards

Conflict of interest The authors have no conflicts of interests to disclose.

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